IN THE SPECIFICATION:

Please amend paragraph **[0004]** as follows:

[0004] Less invasive indicator dilution methods that do not require that a catheter pass through the valves of the right side of the heart have also been developed. These less invasive methods include the so-called "transpulmonary indicator ~~methods",~~ methods," which include the placement of probes in the esophagus or trachea (e.g., in Doppler/Transesophageal echocardiography). While the use of esophageal or endotracheal probes may seem less invasive than the introduction of a catheter into the heart of a patient, the potential for harming a patient exists nonetheless.

Please amend paragraph **[0009]** as follows:

[0009] The carbon dioxide Fick equation (1) and the differential Fick carbon dioxide equation (2) each require a determination of the VCO_2 of a patient. Carbon dioxide elimination is the net volume of carbon dioxide produced by the patient, or excreted from the body of a patient, during respiration. Therefore, carbon dioxide elimination is useful as an indicator of the metabolic rate of the patient. The VCO_2 of a patient may be noninvasively measured as the difference, per breath, between the volume of carbon dioxide inhaled during inspiration and the volume of carbon dioxide exhaled during expiration. Carbon dioxide elimination over a breath is typically calculated as follows:

$$VCO_2 = \int_{breath} V \times f_{CO2}\, dt, \qquad (3)$$

where V is the measured respiratory flow and f_{CO2} is the substantially simultaneously detected carbon dioxide signal, or fraction of the respiratory gases that comprises carbon dioxide, or "carbon dioxide ~~fraction".~~ fraction."

Please amend paragraph **[0014]** as follows:

[0014] In one example of a known differential Fick technique for inducing a change in the effective ventilation of a patient, carbon dioxide may be added to the gases that are inhaled by the patient, either directly (e.g., by the addition of carbon dioxide from a cylinder or other

external source) or by causing a patient to rebreathe previously exhaled gases. An exemplary differential Fick technique that has been employed, which is disclosed in Gedeon, A. et al. in 18 *Med. & Biol. Eng. & ~~Comput.~~ Comput.*, 411-418 (1980) (hereinafter "Gedeon"), employs a period of increased ventilation followed immediately by a period of decreased ventilation. When the technique disclosed in Gedeon or another so-called "rebreathing" process is used, the V_{CO_2} of the patient decreases to a level that is less than that which is measured during normal breathing. Rebreathing during which the V_{CO_2} decreases to near zero is typically referred to as "total ~~rebreathing".~~ rebreathing." Rebreathing that causes some decrease, but not a total reduction of V_{CO_2}, is typically referred to as "partial-~~rebreathing".~~ rebreathing." These rebreathing processes may be used either to noninvasively estimate the $CvCO_2$, as in "total-~~rebreathing",~~ rebreathing," or to obviate the need to know $CvCO_2$, as in "partial-~~rebreathing".~~ rebreathing."

Please amend paragraph **[0016]** as follows:

[0016] During total rebreathing, substantially all of the gas inhaled by the patient was expired during the previous breath. Thus, during total rebreathing, $PetCO_2$ is typically assumed to be equal or closely related to the partial pressure of carbon dioxide in the arterial ($PaCO_2$), venous ($PvCO_2$), and alveolar ($PACO_2$) blood of the patient. Total rebreathing processes are based on the assumption that neither the pulmonary capillary blood flow or cardiac output, nor the $CvCO_2$ of the patient, changes substantially during the rebreathing process. The partial pressure of carbon dioxide in blood may be converted to the content of carbon dioxide in blood by means of a carbon dioxide dissociation curve, where the change in the carbon dioxide content of the blood ~~($CvCO_2$ - $CaCO_2$)~~ ($CvCO_2$ - $CaCO_2$) is equal to the slope(s) of the carbon dioxide dissociation curve multiplied by the measured change in $PetCO_2$, as caused by a change in effective ventilation, such as rebreathing.

Please amend paragraph **[0018]** as follows:

[0018] As an example of a known partial rebreathing process, the NICO™ system offered by Novametrix Medical Systems Inc. of Wallingford, Connecticut, employs a 60 second

baseline period, a 50 second rebreathing period, and a 70 second recovery period. The complete rebreathing cycle lasts for about three minutes. Another exemplary partial rebreathing process is disclosed in Capek, JM, and Roy, RJ, Noninvasive measurement of cardiac output using partial CO_2 ~~rebreathing IEEE Trans Biomed Eng~~ rebreathing, IEEE Trans. Biomed. Eng. 1988; 35:653-661. That rebreathing process has a total cycle time of about 3½ minutes, with the actual rebreathing phase lasting for about 30 seconds. Gama de Abreu, M, et al., Partial carbon dioxide rebreathing: A reliable technique for noninvasive measurement of nonshunted pulmonary capillary blood flow, Crit. Care Med. 1997; 25: 675-683, discloses a rebreathing process with a 35 second rebreathing phase and a total cycle time, including baseline and recovery phases, of about 3 minutes.

Please amend paragraph **[0024]** as follows:

[0024] The present invention includes a differential Fick technique for noninvasively determining the pulmonary capillary blood flow or cardiac output of a patient. The differential Fick method of the present invention includes two phases: a "normal" respiration phase and a phase in which a change in the effective ventilation of a patient is induced, which phase is referred to herein as a "change-inducing ~~phase".~~ phase." These phases are abbreviated in duration relative to similar phases in known differential Fick techniques. The phases of the inventive differential Fick technique may be repeatedly cycled, or oscillated, with the durations of the normal respiration phase and the change-inducing phase being substantially the same.

Please amend paragraph **[0026]** as follows:

[0026] In another aspect of a differential Fick technique incorporating teachings of the present invention, the durations of the normal respiration and change-inducing phases are abbreviated relative to the time lengths of the corresponding phases in conventional differential Fick techniques. For example, each phase may have a duration of about 30 seconds. The length of an entire cycle of the differential Fick technique, measured as the difference in time between the end of one change-inducing phase and the end of another, immediately subsequent ~~change-~~

~~inducing~~ change-inducing phase is also shortened relative to the durations of conventional cycles of comparable differential Fick techniques. For example, a differential Fick technique conducted in accordance with teachings of the present invention may have a cycle time of about two minutes or less.

Please amend paragraph **[0039]** as follows:

[0039] FIGs. 8A and 8B are two-dimensional plots illustrating an exemplary rebreathing technique and an accompanying method for modifying respiratory data to obtain an accurate ~~best-fit~~ best-fit line therethrough;

Please amend paragraph **[0047]** as follows:

[0047] Of course the change between the first and second ventilation states may be either abrupt, as depicted in FIG. 9B, or gradual. For example, when the change ~~the~~ in the effective ventilation of a patient is a change in the tidal volume of a patient, the change or oscillation between a minimum tidal volume and a maximum tidal volume may follow a sinusoidal curve (e.g., 400 ml, 410 ml, 420 ml, . . . 580 ml, 590 ml, 600 ml, 590 ml, 580 ml, . . . 420 ml, 410 ml, 400 ml, 410 ml, 420 ml, . . .).

Please amend paragraph **[0052]** as follows:

[0052] Another aspect of the present invention is related to a discovery of the inventors herein that, in order to accurately, noninvasively measure pulmonary capillary blood flow or cardiac output, a recovery period is not necessary following the change in the effective ventilation of the patient. Accordingly, differential Fick techniques incorporating teachings of the present invention may lack the conventional recovery or stabilization period that typically follows inducement of a change in the effective ventilation of a patient. The first and second phases may be continuously cycled, one (e.g., the first phase) immediately following completion of the other (e.g., the second phase). In addition, respiration (e.g., flow and carbon dioxide or oxygen levels) of the patient ~~maybe~~ may be continuously evaluated or monitored while the

differential Fick technique of the present invention is being effected. Alternatively, one or more intermittent measurements may be obtained during each immediately sequential occurrence of the first and second phases.

Please amend paragraph **[0053]** as follows:

[0053] As an example of a differential Fick technique incorporating teachings of the present invention, partial rebreathing may be employed. In the partial rebreathing embodiment of the differential Fick technique, the first phase is a rebreathing phase, while the second phase is a ~~non-rebreathing~~ nonrebreathing phase. In rebreathing, the VCO_2 of a patient is measured along with the $PetCO_2$ of the patient or another indicator of the carbon dioxide content of the patient's blood (e.g., $CaCO_2$, pCO_2, a surrogate of $PetCO_2$, such as the average pCO_2 over about the last 5% of the expired volume, etc.).

Please amend paragraph **[0056]** as follows:

[0056] Flow sensor 12 and carbon dioxide sensor 14 are connected to a flow monitor 16 and a carbon dioxide monitor 18, respectively, each of which may be operatively associated with a computer 20 so that data from the flow and carbon dioxide monitors 16 and 18 representative of the signals from each of flow sensor 12 and carbon dioxide sensor 14 may be detected by computer 20 and processed according to programming (e.g., by software) thereof. Preferably, raw flow and carbon dioxide signals ~~from the~~ from flow monitor 16 and carbon dioxide sensor ~~are~~ 14 are filtered to remove any significant artifacts. As respiratory flow and carbon dioxide pressure measurements are made, the respiratory flow and carbon dioxide pressure data may be stored by computer 20.

Please amend paragraph **[0058]** as follows:

[0058] In order to effect rebreathing, a deadspace 22, or carbon dioxide source, communicates with the airway of patient 10. During the ~~non-rebreathing~~ nonrebreathing phase, communication between deadspace 22 and the airway of patient 10 is interrupted.

Please amend paragraph **[0059]** as follows:

[0059] In partial rebreathing in accordance with teachings of the present invention, a baseline may be established during the ~~non-rebreathing~~ nonrebreathing phase, in which carbon dioxide elimination and the partial pressure of end tidal carbon dioxide are measured. The ~~non-rebreathing~~ nonrebreathing phase is then immediately followed by a rebreathing phase, wherein a change in the $CaCO_2$ of the patient is induced and VCO_2 and $PetCO_2$ are again measured. The rebreathing phase is then immediately followed by another ~~non-rebreathing~~ nonrebreathing phase, wherein VCO_2 and $PetCO_2$ are again measured.

Please amend paragraph **[0060]** as follows:

[0060] The differential Fick technique of the present invention may be used with conventional rebreathing maneuvers and processes, as well as other known rebreathing maneuvers and processes, which are modified by either shortening or completely eliminating the conventional recovery or stabilization periods of these maneuvers and processes. For example, the differential Fick technique of the present invention may be used with the so-called "bi-directional" process disclosed in U.S. ~~patent application serial no.~~ Patent Application Serial No. 09/150,136, filed September 9, 1998, now U.S. Patent No. 6,238,351, issued May 29, 2001 (hereinafter "the ~~'136 Application"),~~ '351 Patent"), the disclosure of which is hereby incorporated in its entirety by this reference, or in the so-called "best-fit line" method, which is disclosed in U.S. ~~patent application serial no.~~ Patent Application Serial No. 09/510,702, filed on February 22, 2000, now U.S. Patent No. 6,540,689, issued April 1, 2003 (hereinafter "the ~~'702 Application"),~~ '689 Patent"), the disclosure of which is hereby incorporated in its entirety by this reference.

Please amend paragraph **[0061]** as follows:

[0061] In the bi-directional rebreathing process, as disclosed in the ~~'136 Application,~~ '351 Patent, respiratory carbon dioxide and flow measurements are obtained in three phases: a

"before" rebreathing phase, a "during" rebreathing phase, and an "after" rebreathing phase. When teachings of the present invention are applied to the bi-directional rebreathing method, measurements obtained during a first ~~non-rebreathing~~ nonrebreathing phase provide data for the "before" rebreathing period of a first rebreathing cycle, measurements obtained in the rebreathing phase provide data for the "during" rebreathing period of the first rebreathing cycle, and measurements obtained during the next ~~non-rebreathing~~ nonrebreathing phase provide data for both the "after" rebreathing period of the first rebreathing cycle and the "before" rebreathing period of the next rebreathing cycle.

Please amend paragraph **[0067]** as follows:

[0067] Since $CvCO_2$ may change over time, an accurate noninvasive Fick-based determination of the pulmonary capillary blood flow or cardiac output of a patient may include an estimation of the rate at which $CvCO_2$ changes. With an exemplary assumption that changes in $CvCO_2$ are substantially linear over the rebreathing cycle and, therefore, that the rate of change is constant, the rate of change in $CvCO_2$, represented as ~~"k",~~ "k," may be determined with the following equation:

$$k = \frac{\Delta CvCO_2}{\Delta t.} \qquad (10)$$

Alternatively, the change in carbon dioxide content of the venous blood may be assumed to substantially follow a curve of some other shape that is reasonably based on the character of the change in carbon dioxide content, such as an exponential curve, wherein the rate of change would also be exponential, or the curve of a polynomial. As another alternative, the rate of change in $CvCO_2$ may be approximated by an artificial neural network or a radial basis function, as known in the art.

Please amend paragraph **[0068]** as follows:

[0068] When the change in $CvCO_2$ is assumed to be linear with respect to time and, therefore, the rate of change of $CvCO_2$ is assumed to be constant, the change in $CvCO_2$ between

the "before" and "during" phases and between the "during" and "after" phases can be expressed by the following equations:

$$\Delta CvCO_{2\,BD} = k(t_B - t_D) \tag{11}$$

and

$$\Delta CvCO_{2\,DA} = k(t_D - t_A), \tag{12}$$

where t_D, t_B and t_A represent the times at which the ~~"before",~~ "before," "during" and "after" phases respectively occur.

Please amend paragraph **[0069]** as follows:

[0069] The foregoing equations for the change in $CvCO_2$ may be substituted into the differential form of the carbon dioxide Fick equation that considers the breathing of a patient during each of the ~~"before",~~ "before," "during" and "after" phases and the "Δ" terms expanded to yield the following form of the carbon dioxide Fick equation, which accounts for any changes in $CvCO_2$ and is, therefore, useful in the bi-directional rebreathing method:

$$Q = \frac{VCO_{2\,B} + VCO_{2\,A} - 2 \cdot VCO_{2\,D}}{k \cdot (t_B + t_A - 2 \cdot t_D) - (CACO_{2\,B} + CACO_{2\,A} - 2 \cdot CACO_{2\,D}).} \tag{13}$$

If, however, $t_D - t_B = t_A - t_D$ as is probable in the differential Fick technique of the present invention, then $t_A + t_B = 2 \cdot t_D$, and it would not be necessary to calculate k, as k would be multiplied by zero. Accordingly, if $t_D - t_B = t_A - t_D$, such as when the durations of the first and second phases are the same, the following equation could be employed to determine the pulmonary capillary blood flow of a patient:

$$Q = \frac{VCO_{2\,B} + VCO_{2\,A} - 2 \cdot VCO_{2\,D}}{-(CACO_{2\,B} + CACO_{2\,A} - 2 \cdot CACO_{2\,D}).} \tag{14}$$

Please amend paragraph **[0071]** as follows:

[0071] *Use of the Bi-Directional Rebreathing Technique While Cardiac Output is Changing to Noninvasively Determine Pulmonary Capillary ~~Blood~~ Blood Flow*

Please amend paragraph **[0078]** as follows:

[0078] In practicing the bi-directional rebreathing method, a system such as that described in reference to FIG. 1 is used and the patient's breathing is monitored during rebreathing and ~~non-rebreathing~~ nonrebreathing phases to detect the amount of CO_2 exhaled by the patient and the flow rate of the patient's respiration during these phases, from which V_{CO_2} and $CvCO_2$ may be determined.

Please amend paragraph **[0082]** as follows:

[0082] The $PetCO_2$ of the patient is also measured for each of the ~~"before",~~ "before," "during" and "after" phases. As $PetCO_2$, when corrected for parallel deadspace (of nonperfused alveoli), is assumed to be equal to the partial pressure of carbon dioxide in the alveolar blood (P_ACO_2) and the partial pressure of CO_2 in the arterial blood ($PaCO_2$), a carbon dioxide dissociation curve may be employed with the end tidal carbon dioxide partial pressure measurements, as known in the art, to determine the content of carbon dioxide in blood of the alveoli (C_ACO_2) of the lungs of the patient that participate in the exchange of blood gases, which alveoli are typically referred to as "perfused" alveoli, for each of the before, during, and after rebreathing phases. C_ACO_2 is assumed to be equal to the content of carbon dioxide in the arterial blood ($CaCO_2$). FIG. 4 is a graph that illustrates the $PetCO_2$ measured during each of the before, during, and after phases of the rebreathing process of the present invention.

Please amend paragraph **[0084]** as follows:

[0084] In determining the pulmonary capillary blood flow or cardiac output of a patient when $CvCO_2$ changes, the differences between V_{CO_2} before rebreathing and during rebreathing, which difference is also referred to as ~~"$\Delta V_{CO_{2\,BD}}$",~~ "$\Delta V_{CO_{2\,BD}}$," and during rebreathing and after rebreathing, which difference is also referred to as ~~"$\Delta V_{CO_{2\,DA}}$",~~ "$\Delta V_{CO_{2\,DA}}$," are determined. The differences between the C_ACO_2 before and during rebreathing, which difference is also referred to as ~~"$\Delta C_ACO_{2\,BD}$",~~ "$\Delta C_ACO_{2\,BD}$," and during rebreathing and after rebreathing, which difference is also referred to as ~~"$\Delta C_ACO_{2\,DA}$",~~ "$\Delta C_ACO_{2\,DA}$," are also determined.

Please amend paragraph **[0088]** as follows:

[0088] By way of contrast with the use of measurements at the plateaus of each of the phases, as depicted in FIGs. 2A and 2B, in conventional rebreathing processes and the bi-directional rebreathing process, V_{CO_2} and carbon dioxide content data are continually measured in the rebreathing method of the ~~'702 Application.~~ '689 Patent. As a result, a plot of the measurements may have the appearance of the graph shown in FIG. 5A, with data at 100 being based on before rebreathing measurements, data along arrow 102 being based on during rebreathing measurements, and data along arrow 104 being based on after rebreathing measurements. These data may be obtained by use of a single rebreathing cycle, over the course of a number of rebreathing cycles, at one or more discrete time intervals, or on a breath-by-breath basis, where data is continually measured, calculated, and analyzed in accordance with the method of the invention so as to continually update or monitor the pulmonary capillary blood flow or cardiac output of a patient.

Please amend paragraph **[0091]** as follows:

[0091] Once respiratory carbon dioxide pressure and flow measurements have been made, as depicted in FIG. 1, during both the first (e.g., rebreathing) and second (e.g., ~~non-rebreathing)~~ nonrebreathing) phases, these respiratory carbon dioxide pressure and flow data are used, as known in the art, to calculate V_{CO_2} and $PetCO_2$, as well as the changes in V_{CO_2} and $PetCO_2$ that occur with the change in effective ventilation.

Please amend paragraph **[0094]** as follows:

[0094] For example, the equation for the ~~best-fit~~ best-fit line is:

$$y = mx + b \tag{37}$$

or

$$m = \frac{y - b}{x}, \tag{38}$$

where y is the y-axis ordinate of a data point, x is the x-axis ordinate of the same data point, m is the slope of the line, and b is the offset value for the line. If VCO_2 is measured on the y-axis and $CaCO_2$ is measured on the x-axis, then

$$m = \frac{VCO_2 - b}{CaCO_2} \quad . \tag{39}$$

The negative slope (i.e., -1 × m) of the best-fit line through the VCO_2-$CaCO_2$ data would be equal to the pulmonary capillary blood flow or cardiac output of the patient:

$$-m = Q. \tag{40}$$

Please amend paragraph **[0102]** as follows:

[0102] As an example of one way in which an optimal filter coefficient may be selected, α is first set to a default value (e.g., 0.85) and the calculated VCO_2 or $CaCO_2$ values are filtered on the basis of the default filter coefficient, α. The linear regression is then performed to obtain a best-fit line. If the correlation coefficient of the best-fit line calculated with the just-filtered data is less than the correlation coefficient of the immediately preceding best-fit line, which was calculated with unfiltered data or with a prior filter coefficient, then a predetermined α adjustment value (e.g., 0.01) is changed by multiplying the α adjustment value by -1 and by modifying the filter coefficient by adding the modified α adjustment value thereto. Otherwise, the filter coefficient, α, is modified by adding the unmodified α adjustment value thereto. The process of filtering the data based on a modified filter coefficient, obtaining a best-fit line for the data, comparing the correlation coefficient of the best-fit line to the correlation coefficient of the previous best-fit line, and adjusting the filter coefficient accordingly is then repeated a predetermined number of times (e.g., 50 times). The best-fit line with the greatest correlation coefficient, based on the unfiltered data and each set of filtered data, is selected to calculate the pulmonary capillary blood flow or cardiac output of the patient. When filtering is used, the ~~VCO_2-$CaCO_2$~~ VCO_2-$CaCO_2$ plot preferably narrows, as depicted in FIGs. 5B and 7, to thereby increase the accuracy with which the location and orientation of a best-fit line can be established and, thus,

to increase the accuracy of a pulmonary capillary blood flow or cardiac output determination based on the data.

Please amend paragraph **[0103]** as follows:

[0103] Another example of a method for increasing the correlation coefficient between the V_{CO_2} and $CaCO_2$ data and the best-fit line therefor, which is referred to herein as ~~"clustering",~~ "clustering," includes the selection of data points that are grouped closely together. That is, the data points that are selected include those data points having a number of other data points within a predetermined range thereof. Data points that are not clustered are probably inaccurate or based on measurements taken during spurious breaths. As an accurate best-fit line through the data would likely be based on the clustered data, the data points that are not located in a cluster are not used in calculating the location and orientation of a ~~best-fit~~ best-fit line for the data.

Please amend paragraph **[0111]** as follows:

[0111] As shown in FIGs. 8A and 8B, a line or the equation for a line 110 representing a minimum expected pulmonary capillary blood flow (i.e., $-m_{line} = PCBF_{min}$) and a line or the equation for a line 120 representing a maximum expected pulmonary capillary blood flow ~~(i.e., $m_{line\ 120} = PCBF_{max}$)~~ (i.e., $-m_{line\ 120} = PCBF_{max}$) are positioned to intersect at a data point 130. For example, when the x-ordinate is based on $CaCO_2$, line 110 may have a slope of -0.5, which represents a minimum expected pulmonary capillary blood flow of 0.5 L/min, and line 120 may have a slope of -20, which represents a maximum pulmonary capillary blood flow of 20 L/min. Of course, other pulmonary capillary blood flow values for lines 110 and 120 may also be used.

Please amend paragraph **[0116]** as follows:

[0116] As an example of the use of filtering and clustering together, the calculated V_{CO_2} data are grouped together as the y-axis data of a two-dimensional line graph and the calculated $CaCO_2$ data points are grouped together as x-axis data points. The data points in at

least one of the groups are filtered to determine a best-fit line for the data having an optimum correlation coefficient. The data are also clustered, either before or after filtering, to further improve the correlation coefficient of the best-fit line to the calculated V_{CO_2} and $CaCO_2$ data. The remaining data is then used to determine (e.g., by linear regression) a best-fit line therefor, as well as a correlation coefficient for the ~~best fit~~ best-fit line. The slope of the ~~best fit~~ best-fit line is then calculated and used to determine pulmonary capillary blood flow or cardiac output. The correlation coefficient may also be used to indicate the reliability of the pulmonary capillary blood flow or cardiac output determination or to impart a specific weight to the pulmonary capillary blood flow or cardiac output determination in a weighted average thereof.

Please amend paragraph **[0117]** as follows:

[0117] Once the location and orientation of an accurate best-fit line for the data has been determined, as disclosed previously herein, the pulmonary capillary blood flow of the patient can be calculated as the negative of the slope of the ~~best fit~~ best-fit line.